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12-9-2022

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Recommended Citation

Marshall, Patricia, Craig, Kaitlynn P., and Hyun, Insoo, "Moral Status and the Oversight of Research Involving Chimeric Animals," in *Creating Chimeric Animals: Seeking Clarity on Ethics and Oversight*, ed. Karen J. Maschke et al., special report, *Hastings Center Report* 52, no. 6 (2022): S41–S45. DOI: [10.1002/hast.1431](https://doi.org/10.1002/hast.1431)

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Moral Status and the Oversight of Research Involving Chimeric Animals

BY PATRICIA MARSHALL, KAITLYNN P. CRAIG, AND INSOO HYUN

Concerns around the use of nonhuman animals in research have been a rich source of bioethical and scientific debate, both historically and at present. In our view, a key issue is not whether nonhuman research animals have moral status tout court but whether their level of moral status is sufficient to rule out their use and destruction for scientific research. Most people would agree that nonhuman animals have at least some degree of moral status grounded in their sentience—that is, their capacity to experience pleasure and pain. Indeed, sentience is what ethically justifies the regulatory requirements enforced by institutional animal care and use committees (IACUCs) in the United States and by their equivalents abroad. However, current research practices posit that sentience alone is not sufficient to prohibit the use of nonhuman research animals, as long as proper measures are taken by researchers to administer analgesics and use other strategies to uphold animal welfare requirements. In other words, current research environments do not prohibit the sacrifice and use of approved nonhuman animal species for biomedical research, even if one grants that these species possess a degree of moral status consistent with their sentience.

It is against this backdrop of common research practice that we consider the oversight and use of nonhuman animals in stem cell research. Studies involving the trans-

fer of human stem cells or their direct derivatives into nonhuman animal hosts—what are often called “chimeric animals”—has been a staple in stem cell science for over two decades.

Correspondingly, this subset of animal research has also served as a staple in the general ethical discourse around research with nonhuman animals. For example, one commentator has worried that chimeras might acquire biological changes that would enhance their baseline species’ moral status.¹ Another has argued that the moral status of “part-human beings” should be grounded not in sentience or the acquisition of humanlike properties but, rather, in the “phenomenal value” of their mental experiences. According to this view, changes to the moral status of part-human beings would be caused by direct changes to such phenomenal value via the transfer of human cells.²

Although moral status—or more specifically, for our purposes, conceptualizing *changes* to the moral status of these modified research animals—is a frequent topic in the bioethics and philosophical literature and holds a prominent role in ethical debates over human–nonhuman-animal chimeric research, the concept remains quite hazy in the conduct and oversight of such research. Two sets of influential guidelines exist for human-animal chimeric research and oversight. One set is from the U.S. National Academies of Sciences, Engineering, and Medicine, released in 2005³ and updated in 2010,⁴ and the other from the International Society of Stem Cell Research, originally released in 2006⁵ and updated in 2016⁶ and 2021.⁷ These sets of guidelines represent

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important landmarks in U.S. and international initiatives. However, the NASEM guidelines and the earlier versions of the ISSCR guidelines (prior to 2021)—which regulators have been mainly relying on at the time of this writing—are vague and hard to operationalize. As just one example, the 2016 ISSCR guidelines⁸ hold that human-animal chimeric research triggers special review by a stem cell oversight committee “when the degree of functional integration is considerable enough to raise concerns that the nature of the animal host may be substantially altered,” but they do not clarify what would count as altering the nature of an animal host.

It remains unclear what is meant by a “change in the moral status” of modified animals in the oversight of stem cell-based human-animal chimeric research. In this essay,

we present findings from interviews we conducted with scientists, members of embryonic stem cell research oversight (ESCRO) committees, and IACUC members at eleven institutions in different areas of the United States where stem cell-based human-nonhuman chimeric research is being conducted. (See the box for a description of the methods used in this study.) Abstract conceptions of what is involved in moral-status change are unhelpful for persons involved in stem cell transfer research and oversight, especially if the purported grounds for moral-status change are not directly observable or measurable, as with the “phenomenal value” of other nonhuman animals’ mental experiences. Likewise, attempts to analyze changes in moral status, by appealing to related concepts such as consciousness and humanization, for instance, invite many more questions than answers.

Box 1. Methods

A total of thirty-five interviews were conducted from March 2019 through May 2020 with twelve members of ESCRO committees, nine members of IACUCs, and fourteen scientists involved in human–nonhuman-animal chimeric research across the continental United States. At each site chosen, there was always at least one interview with an ESCRO committee member, one with an IACUC member, and one with a scientist. Interviews addressed experiments conducted at the institution, satisfaction with current oversight committees, animal welfare, and conceptual issues associated with moral status and humanization of chimeric animals. The interview guide was pretested and revised. Participants were recruited using snowball sampling techniques. The total number of interviews was capped when we reached a level of saturation regarding the domains of inquiry for the interviews.

This study was approved by Case Western Reserve University’s institutional review board. Every participant was given an information sheet describing the study, and verbal consent was recorded at the beginning of each interview. Participants received a \$50 gift card upon completion of the interview.

Interviews were audiotaped and transcribed. A grounded-theory approach¹ was employed in data analysis. Thematic domains were identified through a process of systematic review of transcripts; a coding dictionary was developed and expanded with continual content analysis. Interviews were independently coded by two research staff members, and consensus coding was used if there was a disagreement.

1. J. M. Corbin and A. L. Strauss, *Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory* (Thousand Oaks, CA: Sage, 2014).

Findings

Scientists and members of ESCRO committees and IACUCs were asked about how they would assess changes in the moral status of human-animal chimeric animals. Analysis of interview data revealed that most believed moral status is an ambiguous concept that is difficult to define, especially when trying to assess enhanced moral status in chimeric animals. We identified three primary thematic domains regarding moral status: lack of conceptual clarity, consciousness, and humanization. Taken together, these thematic domains illustrate challenges associated with defining changes in moral status, diminishing its usefulness in the context of human–nonhuman-animal chimeric research. Quotations from the interviews reflect beliefs about these three dimensions of moral status; each quotation is identified as the view of a scientist or of a member of an ESCRO committee or IACUC.

Lack of conceptual clarity. Overall, the scientists and members of ESCRO committees and of IACUCs noted that the notion of changed moral status is a vague and uncertain concept in human-animal chimeric research. A number of interviewees were very direct in calling attention to the lack of conceptual clarity regarding changes in moral status. A member of an ESCRO committee reported, “Well, honestly, I think that we don’t know what we’re talking about when we start to use that language.” Another member of an ESCRO committee asked what it takes to make an animal human, calling into question the issue of what changes in moral status means: “I don’t know what moral status really means. I don’t think putting a human cell into an animal makes that animal human.” A scientist noted that lack of definitional clarity may reduce the ability to reach consensus about knowing when investigators have the potential to “cross a line” in human-animal chimeric research:

A scientist observed that the essential element in consciousness is not about the number of human cells transferred to an animal but about the ability to think. “What you really want to know is, ‘Okay, is it thinking anything? And is it thinking that it would rather not be in this experiment?’”

I think that the most bright-line points are contribution to the germ line and the possibility for animals getting together doing something really interesting. Or contributions to the central nervous system and creating a different sort of conceptual state in terms of how the animal thinks. I think the first one is actually quite easy to control, if you keep animals apart. The second one is very, very fuzzy. That’s the one where I have the hardest time landing on a set of criteria that even the majority of people would agree to, to make the line, much less to know when we’ve crossed it.

Individuals representing all groups agreed, noting that uncertain conceptualizations of enhanced moral status are associated with a lack of clarity in knowing when a chimeric animal has reached a point where a prohibitive degree of moral status may be applicable. For example, an ESCRO committee member said, “[Y]ou’re looking at a mouse that’s been injected with these cells, how do you look at them and tell them they’re morally different? We try to use real concrete things, the integration of the cells or maybe seeing development of different things to see. Yeah, there’s really not a lot of clarity on how you actually would do that.”

Several interviewees emphasized that the lack of clarity is directly related to subjectivity in defining moral status. A scientist noted, “The moral status is something—to me, it’s complicated because it’s so subjective.” Another scientist stated that subjectivity in definitions about moral status can limit what may be actionable in relation to human-animal chimeric research: “People may have a different idea what the moral status of those animals [is] in the first place and how it’s changed. I think it’s definitely not super actionable.”

Consciousness. Analysis of discussions of enhanced moral status in human–nonhuman-animal cell transfer research included references to consciousness and, in particular, the potential to experience suffering. Interviewees from all groups called attention to the porous and ambiguous boundaries in deciding what consciousness means for human-animal chimeric research. An ESCRO com-

mittee member, for example, explained, “To me, it’s not about their moral status; it’s really about their ability to understand, to either feel and/or perceive their conditions.” Similarly, a member of an IACUC said, “I guess when I hear [‘moral status’] . . . , I think people are concerned about will this animal become sentient in the way that people are? Have that sort of awareness? Of course, we don’t know what sort of awareness animals have, but . . . I think people are concerned that it’ll be a human consciousness inside an animal’s body. Maybe not completely but approaching that.”

A scientist observed that the essential element in consciousness is not about the number of human cells transferred to an animal but, rather, about the ability to think. “To make this as stark as possible, it’s not just about the percentage of neurons, for example, that are human in the animal. Or the layers of the brain that they’re in or even how they’re interconnected. What you really want to know is, ‘Okay, is it thinking anything? And is it thinking that it would rather not be in this experiment?’”

A member of an ESCRO committee called attention to the range of meanings surrounding people’s notions of consciousness in human and nonhuman animals: “Animals already possess certain kinds of consciousness, different from human maybe, maybe as sophisticated as human in different ways. Nobody really knows what they’re talking about when they just say the word ‘consciousness.’ I don’t think that saying, ‘Well, as long as the animal doesn’t become conscious,’ it’s okay because we just don’t really know what that word even means or what consciousness might look like in different species.”

Highlighting the ambiguity associated with defining changes in moral status and consciousness, an ESCRO committee member pondered, “Does it [‘moral status’] refer to the phenomenon of consciousness? Does it refer to self-awareness? Does it refer to a certain sort of intellectual capacity? You got birds that can navigate themselves from the North Pole to South America. Unbelievable neurologic feats that humans cannot even approach. It sounds crazy, but I think we have no idea . . . what that word [‘moral

status'] means. I think consciousness is the one that most people are thinking about."

Overall, scientists and members of ESCRO committees and IACUCs called attention to the direct relationship between consciousness and the capacity for suffering. One ESCRO committee member stated, "When we think about use of animals in research, we think about their intelligence and their capacity for suffering ... their ability to anticipate suffering." Another noted, "If you're talking about partially humanizing the neurons in a monkey brain, for example, where the architecture is more similar to ours ... , you might worry that you would create a brain that was more able to suffer than an ordinary monkey's brain." Similarly, a member of an ESCRO committee said, "If you were to abolish the fourteen-day rule and introduce human embryonic stem cell-derived nerves into the brain of a mammal with brain architecture similar to ours, there is some risk that you would increase its cognitive ability in some way. Enable it to suffer more than it can currently suffer."

Interviewees noted the complex connections between beliefs about changes in moral status, cognition, and suffering. An ESCRO committee member said, "My understanding is moral status is based on almost its humanness.... [W]ill they [cell-transfer animals] have human characteristics and that somehow makes things better or worse? [For example,] ... its ability to feel pain, to be conscious of being in pain." Illustrating concerns about moral status, consciousness, and suffering, a scientist reported, "I think it's this notion that if you transplant human neurons into any sort of animal brain, but particularly primates, that there might be some effect unknown of the consciousness of the animals that would be causative of suffering in the animals. I think, ultimately, when we talk about the moral status of the animals, we really are trying to limit suffering caused by our experimentation." Similarly, a scientist noted, "There's a huge scientific barrier for achieving an organism that would have an altered moral status [I]f you made a human monkey chimera, there is a chance that that organism would have an altered moral status. I think right now what we've thought is the most troubling aspect would be if the animal had an enhanced capacity for suffering, so this would be something like being able to anticipate something, anticipating suffering or having memories of suffering. The nature of an animal suffering could be altered if it acquired more humanlike capacities."

Humanization. The concept of humanization was discussed by individuals in all groups interviewed, and they highlighted the lack of specificity regarding what this means in human-animal chimeric research. This vagueness has implications for assessments of enhanced moral status and consciousness in chimeric animals. Speaking directly to the definitional ambiguity surrounding humanization,

a scientist said, "I think people will define that [humanization] depending on the research they are doing. I think probably from an ethicist's point of view ... [it could be] defined ... in a more clear-cut way, [as] anything with human contribution, but I think then we have to define what human contribution means."

A scientist reported that humanization in chimeric animals could raise concerns about obscuring the lines between different species of animals: "There might be a blurring of human-animal boundaries between the species." However, an IACUC member reported that the potential for altering animal species is unlikely at this point: "The word 'humanized' can be legitimately used in a species that has low contribution of human components.... I don't think we've reached a threshold where there's an animal that appears to be a very different species."

Another IACUC member reported that the concept of humanization lacks relevance in human-animal chimeric research: "It ['humanized'] truthfully doesn't mean that much. It's an adjective to say that there are human cells in an animal. To me, it doesn't make me think that the animals are more human than mouse or more human than [nonhuman] primate."

Interviewees discussed factors that are sometimes thought to contribute to humanization, including the percentage of human cells used in human-animal chimeric research. These comments reflect the notion of humanization as a continuum in chimeric animals. Beliefs about the impact of increasing the number of human cells used in research raise questions about when consciousness becomes an issue for identifying what constitutes *being human*. A member of an ESCRO committee reported, "This gets at the point of what percentage of neurons, for example, in a primitive nervous system would confer human characteristics on a chimera? It's a hypothetical, but at what point would something have a consciousness that we, as humans, could identify with? These are the issues that are really impossible to define quantitatively, but I think some of the issues [are] the percentage of cells." A scientist noted, "I think it really is when do we define or—how much human material has to be there before we declare a host part human, so that's what we would call humanity. All of that, then, plays into the moral implication as to how we define what is human contribution, how much human contribution is required to raise an ethical concern. ... Our moral obligation comes in to understanding what we really call human contribution."

Limitations

Enhanced moral status is a complex concept. In human-animal chimeric research and oversight, it is dependent largely on how people think about and understand what

it means. When delving into the concept of enhanced moral status, our interviewees often transitioned to speaking about consciousness and humanization, themselves concepts quite difficult to articulate, much less measure. Interviewees expressed concerns about the potential for suffering in human-animal chimeric research. Thus, animal welfare—something that can be assessed and improved—is central to investigational practices in human-animal chimeric research.

Our study was conducted with ESCRO members, IACUC members, and scientists involved in human-animal chimeric research in the Northeast and South and on the West Coast, limiting the generalizability of findings. In the future, it would be interesting to conduct research on these issues with the general public, religiously diverse groups of individuals, or scientists representing all geographically different areas of the United States. Our findings, however, suggest that concepts of enhanced moral status and consciousness are not very useful in human-animal chimeric research in part because their meanings are not easily defined, which presents challenges to applying the concepts in research. Instead, scientists and oversight committee members we interviewed seemed to rely on standard assessments of changes in animal welfare when focusing on the ethics of human-animal chimeric research.

Acknowledgment

This work was supported by the National Human Genome Research Institute of the National Institutes of Health under award number R01HG010168.

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2. J. J. Koplin, “Human-Animal Chimeras: The Moral Insignificance of Uniquely Human Capacities,” *Hastings Center Report* 49, no. 5 (2019): 23-32.

3. Institute of Medicine and National Research Council, *Guidelines for Human Embryonic Stem Cell Research* (Washington, DC: National Academies Press, 2005).

4. Institute of Medicine and National Research Council, *Final Report of the National Academies’ Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies’ Guidelines for Human Embryonic Stem Cell Research* (Washington, DC: National Academies Press, 2010).

5. International Society for Stem Cell Research, *Guidelines for the Conduct of Human Embryonic Stem Cell Research* (ISSCR, December 21, 2006), at <https://www.isscr.org/the-archives/#GuidelinesArchive>.

6. International Society for Stem Cell Research, *Guidelines for Stem Cell Research and Clinical Translation* (ISSCR, May 12, 2016), at <https://www.isscr.org/the-archives/#GuidelinesArchive>

7. International Society for Stem Cell Research, *Guidelines for the Field of Stem Cell Research and Regenerative Medicine* (ISSCR, 2021), at <https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation>.

8. International Society for Stem Cell Research, *Guidelines for Stem Cell Research and Clinical Translation*.